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Wayne E. Cascio, MD, FCC, Director
Center for Public Health and Environmental Assessment (CPHEA)
Office of Research and Development (ORD)
Environmental Protection Agency (EPA)
1200 Pennsylvania Ave., NW
Washington, DC 20460

Re: EPA Integrated Risk Information System 2022 Draft Formaldehyde Assessment – Inhalation

Dear Dr. Cascio:

In response to the release of the *Draft Toxicological Review of Formaldehyde – Inhalation* prepared by the U.S. EPA's Integrated Risk Information System (IRIS) program, I respectfully submit the following public comments. Specifically, I highlight the following two publications I authored that EPA failed to properly evaluate and address in the Draft Review:

> Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells? (Mundt et al. 2017); and
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> Six years after the NRC review of EPA's *Draft IRIS Toxicological Review of Formaldehyde*: Regulatory implications of new science in evaluating formaldehyde leukemogenicity (Mundt et al. 2018)

The first publication reports on a fuller statistical analysis of the original data from Zhang et al. 2010 – and on which EPA heavily relies to bolster their conclusion that formaldehyde causes leukemia. The second summarizes much of the new science generated since the NRC peer-review of the previous Draft Review and maps the latest scientific information to many of the NRC criticisms of that Draft Report, some of which remain unchanged.

I trust that EPA will find these comments and the attached copies of the two publications helpful in revising and improving the draft.

Sincerely yours,

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Senior Principal Health Scientist, Cardno ChemRisk

Attachments: Comments on U.S. EPA's Integrated Risk Information System (IRIS) Draft Toxicological Review of Formaldehyde – Inhalation; Mundt et al. (2017, 2018)

Comments on U.S. EPA's Integrated Risk Information System (IRIS) Draft Toxicological Review of Formaldehyde – Inhalation

I appreciate the opportunity to provide public comments on the April 2022 IRIS Draft Review of Formaldehyde – Inhalation, but wish to note that the 60-day public comment period was inadequate for responding more fully and appropriately to such an unnecessarily lengthy document that falls short of professional standards of quality of research and scholarly writing.

I therefore focus narrowly here on EPA's evaluation of the epidemiological literature of lymphohematopoietic malignancies (LHMs) and specifically on EPA's dismissal and/or omission treatment of two publications that are directly relevant to this topic:

> Mundt KA, Gallagher AE, Dell LD, Natelson EA, Boffetta P, Gentry PR. (2017). Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells? Crit Rev Toxicol. 47(7):592-602. doi:10.1080/10408444.2017.1301878 (Mundt et al. 2017); and
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> Mundt KA, Gentry PR, Dell LD, Rodricks JV, Boffetta P. (2018). Six years after the NRC review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity. Regul Toxicol Pharmacol. 92:472-490. doi: 10.1016/j.yrtph.2017.11.006. Epub 2017 Nov 20. PMID: 29158043 (Mundt et al. 2018)

The first publication reports on a fuller statistical analysis of the data from Zhang et al. (2010) – and on which EPA heavily relies to bolster their conclusion that formaldehyde causes leukemia. The new analyses, which never have been scientifically addressed or refuted, **clearly demonstrate that there is no association between formaldehyde exposure and any of the blood or aneuploidy outcomes claimed to support their conclusions**. It remains puzzling why no analyses using the individually measured exposure data for each exposed participant ever were reported by Zhang et al. (2010). It also is hard to understand why the paper was accepted for publication absent any analyses based on the exposure data they collected (three measurements on each exposed worker), especially given that the authors described their valuable exposure measurement efforts in the methods section of the published version. That my analysis of their data (using only average exposure as NCI inexplicitly failed to provide the raw exposure data in our Technology Transfer Agreement) clearly demonstrated no relationship between actual formaldehyde exposure and any of the blood or genetic aneuploidy results, and therefore significantly undermined the authors' conclusions is troubling.

The second publication summarizes much of the new science generated since the NRC peer-review of the previous Draft Review. The scientific efforts to clarify the possible relationship between formaldehyde exposure and myeloid leukemias (AML and CML) as reflected in this body of publications provide valuable insights that should not be overlooked by EPA, especially because they are responsive to the NRC peer-review. Though this publication is not a primary research study, it maps the latest scientific information to many of the NRC criticisms of that

Draft Report. I believe that some of the criticisms have not been addressed and the related conclusions in the Draft Report remain unchanged.

1) The EPA largely disregarded the Mundt et al. (2017) fuller analysis of the Zhang et al. (2010) data.

The EPA 2022 Draft Report continues to rely on a cross-sectional study to support a possible MOA for an association between inhalation exposure to formaldehyde and LHMs, based on what they claim (even in the title of the paper) to be "leukemia-specific chromosome changes in cultured myeloid progenitor cells" (Zhang et al. 2010). Cross-sectional studies are incapable of demonstrating changes in clinical markers but might reflect underlying differences between compared groups. Briefly, the investigators recruited 43 formaldehyde-exposed workers and 51 unexposed workers and compared various blood parameters and indicators of chromosomal anomalies – specifically, monosomy 7 and trisomy 8 – between the groups. Despite reporting that approximately three individual exposure measurements were obtained on each exposed worker (and confirmatory sampling among the unexposed), the investigators presented no analyses or results using these data in their publication (it seems highly unlikely that they did not analyze them). Rather, an 'exposed' group was defined simply as workers in plants with approximately 1-2 ppm on "most days" during screening and who had worked the same job for at least the last 3 months, and the unexposed group were workers in plants with no formaldehyde exposure. Gentry et al. (2013) obtained the study data via a FOI request but were not provided the exposure data. They reported serious deviations between the published protocol for this study and the reported methods in the publication. However, Gentry et al. (2013) were unable to evaluate the potential relationship, if any, between the reported blood and genetic aneuploidy results.

Mundt et al. (2017) requested the exposure data via an NCI Technology Transfer Agreement and was provided the average of the three exposure measures for each exposed worker, but not the individual measurements. Thus, the true range of exposure measurements could not be determined. However, they were able to evaluate the relationship, if any, between the average of the individual formaldehyde exposure measurements and all blood and genetic aneuploidy results (Mundt et al. 2017). These results demonstrated no correlation between formaldehyde exposure level (reportedly over at least a fourfold range) and any of the blood or aneuploidy results. Furthermore, the few assay results generated by tests that met the study protocol (e.g., numbers of cells counted, as pointed out by Gentry et al. (2013) appeared to be related to smoking (but not formaldehyde).

The findings as published by Gentry et al. (2013) and Mundt et al. (2017), pointing out several serious (potentially fatal) problems with Zhang et al. (2010), were not adequately acknowledged, addressed or rebutted in the 2022 Draft. The Draft simply points to a letter to the editor claiming that the actual formaldehyde exposure range was "too narrow" to demonstrate any meaningful exposure-responses:

> The differences in lymphocyte subset levels between exposed and unexposed workers reported by Zhang et al. (2010) were challenged by Mundt et al. (2017) in a reanalysis that did not find evidence of an exposure-response trend within the exposed group, although the difference between unexposed and exposed subjects was reconfirmed. The critique by Mundt was responded to in a letter to the editor by the study investigators who explained that the study was not designed to provide a range of exposures wide enough to evaluate exposure-response relationships given the expected effect size and sample size in the study (Rothman et al., 2017) (footnote d, page 1-145).

The authors of the letter to the editor further emphasized their attempts to control for multiple potential confounders (age, sex, alcohol and tobacco use, recent infections, BMI, and medication use) and claim to have been able to rule out co-exposures, but did not address the potential fundamental differences between the exposed and unexposed groups (irrespective of their formaldehyde or exposure), or the most basic problem of interpreting data obtained at a single point in time as "changes." The simple and incomplete arguments presented by Rothman et al. (2017) appear to have been sufficient for the 2022 Draft to dismiss all of the criticisms, most of which have not been addressed or rebutted, including, e.g., the original authors' decision not to present any of their results based on the individual exposure measurements (note that no other study has performed multiple direct exposure measurements on each exposed worker); justification for deviating from their own protocol; propagating the misleading title of the paper indicating that "changes" in blood and aneuploidy indicators (and assuming that the latter were validly performed and analyzed) could be derived from a simple cross-sectional study of two selected groups; etc. (Gentry et al., 2013; Mundt et al. 2017).

Pira et al. (2017) also offered criticisms of the Zhang et al. (2010) study, and these, too appear to have been ignored. As EPA relies on the Zhang et al. (2010) study, it is important that the potentially fatal flaws in that study be addressed. Some of these concerns are summarized more specifically below and are described in greater detail in the original publications.

Zhang et al. (2010) cultured myeloid progenitor cells from workers claiming to quantify leukemia-specific chromosome "changes", including monosomy 7 and trisomy 8. Assuming that such indicators are leukemia-specific (which remains hypothetical), the cells with DNA damage/chromosomal aneuploidy then presumably would travel to the bone marrow, giving rise to leukemia. To date this hypothesis has not been substantiated and remains speculative.

Zhang et al. (2010) also reported lower WBC, lymphocyte, granulocyte, platelet, RBC, and monocyte counts in the group of exposed workers compared to the group of unexposed workers. If these differences in fact were due to formaldehyde exposure, we would expect to see some sign of differences in these blood parameters across the individually measured formaldehyde exposures. Specifically, Mundt et al. (2017) performed regression analyses on formaldehyde exposed workers for exposure-response relationships for the blood parameters. In log-transformed models adjusted for sex and smoking, WBC, RBC and lymphocyte counts

were lower in exposed compared with unexposed workers; however, the differences were similar in magnitude among the two exposure categories (<1.3 ppm and ≥1.3 ppm). In analyses with formaldehyde modeled as a continuous variable, no significant differences in any of the blood parameters were observed for each 1-ppm increase in formaldehyde, adjusting for smoking and sex. Even if Zhang et al. (2010) felt that the exposure range was inadequate, why did they not present these results with the rest of their analyses and provide as well any explanation for the clear and consistent lack of any associations with formaldehyde exposure?

Additionally, the 2022 Draft does not integrate the fuller analyses of the Zhang et al. (2010) data with results of other studies reporting no exposure-dependent differences in blood parameters and genetic markers of formaldehyde-exposed relative to unexposed workers and other cytogenic studies (Casanova-Schmitz et al. 1984; Heck & Casanova, 2004; Lu et al. 2010) or studies examining chromosomal changes in peripheral blood lymphocytes (Bauchinger & Schmid, 1985; Cheotarev et al., 1986; Pala et al., 2008; Suruda et al., 1993; Thomson et al., 1984; Ying et al., 1999) or cytogenetic studies which show genotoxic effects, but fail to show effects on hematopoietic stem cells (He et al., 1998; Shaham et al., 2002; Yager et al., 1986; Ye et al., 2005). These studies largely align with the results of Mundt et al. (2017) and challenge the interpretation that exposure to formaldehyde may induce chromosome or genotoxic changes in blood or chromosomes.

2) The EPA also disregarded the Mundt et al. (2018) summary of relevant studies published in the 6 years following the NRC review of EPA's *Draft IRIS Toxicological Review of Formaldehyde* and addressing several gaps identified by the NRC.

At the time the EPA 2022 Draft Review was released, six epidemiological studies of workers exposed to formaldehyde reported AML-specific results (Blair et al. 2001, Checkoway et al. 2015, Hauptmann et al. 2009, Meyers et al. 2013; Saberi Hosnijeh et al. 2013; and Talibov et al., 2014). In revising and finalizing the 2010 Draft IRIS Assessment (EPA, 2010), EPA has the opportunity to incorporate new evidence from the studies highlighted by Mundt et al. (2018) and address the many issues raised by the NRC reviews. However, it appears that EPA disregarded Mundt et al. (2018), which, while not a primary study, provides helpful insights into the available epidemiological, animal, and mechanistic literature on formaldehyde and cancer.

The NRC Committee recommended that EPA focus on specific diagnoses of leukemia rather than attempting to draw casual conclusions from an analysis of LHMs as LHMs consist of varying leukemias with differing and unique etiologies. The Committee recommended specific diagnoses such as "acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas"; however, EPA continues to focus on the broader groups such as "myeloid leukemia" and "lymphatic leukemia".

EPA's characterization of the literature published since the 2010 IRIS draft is limited and would have been informed by the summaries provided in Mundt et al. (2018). For example, EPA rated Meyers et al. (2013) as an overall high confidence study stating that " the results at the highest levels of formaldehyde exposure showed an approximately two- to three-fold relative increase

in risk of mortality from myeloid leukemia" (p. 1-444). However Meyers et al. (2013) reported an SMR for AML of 1.22 (95% CI 0.67 – 2.05), indicating no excess of AML deaths. In contrast to EPA's selective reference to one reported results, the study authors noted that they "continue to see limited evidence of an association between formaldehyde and leukemia" and that "the extended follow-up did not strengthen previously observed associations" (Meyers et al. 2013). Contrary to the NIOSH investigators own conclusions, EPA rated this study with high confidence in making their "causal determination" that formaldehyde causes myeloid leukemia.

On the other hand, Coggon et al. (2014) followed a cohort of 14,008 formaldehyde producers and users in the UK and reported no increased mortality from ML (SMR 1.16, 95% CI 0.60-2.20 for background exposure, SMR 1.46, 95% CI 0.84 – 2.36 for low/moderate exposure; and SMR 0.93, 95% CI 0.84 – 2.36 for high exposure, respectively). A nested case control analysis of the 45 ML cases generated an imprecise OR for workers exposed to high concentration of formaldehyde for ≥1 year (OR = 1.77, 95% CI 0.45 – 7.03), however the EPA discounted this study (one of the largest cohorts of formaldehyde users and producers to date) due to "limited power" and "the choice… to classify as highly exposed all workers who ever worked in a highly exposed job even if just for one year out of 20, a methodology that mixes workers with many years of high exposure together with workers with just a single year of high exposure, thereby potentially diluting the strength of the association" (EPA Draft p. 1-444).

Other studies showing no association between AML and exposure to formaldehyde such as Talibov et al. 2014 and Saberi Hosnijeh et al. 2013 also where rated as "low confidence" by the EPA despite (in the case of Talibov et al. 2014) adjusting for exposure to other solvents such as benzene and toluene, and (in the case of Saberi Hosnijeh et al. 2013) finding no increased AML risk among the low-exposure group (after adjustment) and observing no cases of AML in the highest exposure category (Mundt et al. 2018). Furthermore, Mundt et al. (2018) noted that the results of Checkoway et al. (2015) are consistent with Meyers et al. (2013), Saberi Hosnijeh et al. (2013), and Talibov et al. (2014) which "report no significant increase in LHM, specifically AML, among cohorts of workers exposed to formaldehyde" (Mundt et al. 2018 p. 487). However, EPA arrives at a different conclusion in part by either dismissing these results as "low confidence" (in the case of Saberi Hosnijeh et al., 2013 and Talibov et al., 2014) or arriving at contradictory conclusions from those of the authors (in the case of Meyers et al., 2013). EPA concludes that "the available epidemiological studies provide *robust* evidence of an association consistent with causation between formaldehyde exposure and increased risk of myeloid leukemia" (p. 1-452).

Overall, the 2022 Draft does not fully consider or integrate the findings of the fuller analyses that call into question Zhang et al. (2010)'s findings nor does it appropriately integrate evidence from cohort studies reporting ML (and specifically AML) results. The fact remains that there are no studies supporting a MOA for formaldehyde causing leukemias (including AML) and there are several key findings that detract from this hypothesis, e.g., 1) formaldehyde does not form either DNA: protein crosslinks or DNA adducts in bone marrow, 2) exogeneous formaldehyde does not escape the portal of entry, 3) there remains no consistent statistically significant relationships between formaldehyde exposure and chromosome aberrations, sister chromatid

exchanges or micronucleated cells in hematopoietic stem cells as conducted in animals, 4) studies in humans exposed to formaldehyde have failed to find a relationship between exposures and chromosomal changes in peripheral blood lymphocytes and 5) the available epidemiological evidence is consistent with no significant increase in LHM, specifically AML, among formaldehyde-exposed workers.

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